AMINOCAPROIC ACID - aminocaproic acid injection, solution
Hospira

5 g/20 mL (250 mg/mL)
Plastic Fliptop Vial
R_x only

DESCRIPTION

Aminocaproic Acid Injection, USP is a 6-aminohexanoic acid, which acts as an inhibitor of fibrinolysis.
Aminocaproic Acid is soluble in water, acid and alkaline solutions; it is sparingly soluble in methanol and practically insoluble in chloroform.
Aminocaproic Acid Injection, USP, for intravenous administration, is a sterile pyrogen-free solution containing 250 mg/mL of aminocaproic acid and Water for Injection. The solution contains no bacteriostat or antimicrobial agent and is intended for use only as a single-dose injection. When smaller doses are required the unused portion should be discarded. Hydrochloric acid may be added to adjust pH to approximately 6.8 during manufacture.
Its chemical structure is:

$$NH_2 - CH_2 - CH_2 - CH_2 - CH_2 - CH_2 - COOH$$

Molecular Weight: 131.17

The semi-rigid vial is fabricated from a specifically formulated polyolefin. It is a copolymer of ethylene and propylene. The safety of the plastic has been confirmed by tests in animals according to USP biological standards for plastic containers. The container requires no vapor barrier to maintain the proper drug concentration.

CLINICAL PHARMACOLOGY

The fibrinolysis-inhibitory effects of aminocaproic acid appear to be exerted principally via inhibition of plasminogen activators and to a lesser degree through antiplasmin activity. In adults, oral absorption appears to be a zero-order process with an absorption rate of 5.2 g/hr. The mean lag time in absorption is 10 minutes. After a single oral dose of 5 g, absorption was complete (F=1). Mean ± SD peak plasma concentrations (164 ± 28 mcg/mL) were reached within 1.2 ± 0.45 hours. After oral administration, the apparent volume of distribution was estimated to be 23.1 ± 6.6 L (mean ± SD). Correspondingly, the volume of distribution after intravenous administration has been reported to be 30 ± 8.2 L. After prolonged administration, aminocaproic acid has been found to distribute throughout extravascular and intravascular compartments of the body, penetrating human red blood cells as well as other tissue cells. Renal excretion is the primary route of elimination, whether aminocaproic acid is administered orally or intravenously. Sixty-five percent of the dose is recovered in the urine as unchanged drug and 11% of the dose appears as the metabolite adipic acid. Renal clearance (116 mL/min) approximates endogenous creatinine clearance. The total body clearance is 169 mL/min. The terminal elimination half-life for aminocaproic acid is approximately 2 hours.

INDICATIONS AND USAGE

Aminocaproic Acid Injection, is useful in enhancing hemostasis when fibrinolysis contributes to bleeding. In life-threatening situations, fresh whole blood transfusions, fibrinogen infusions, and other emergency measures may be required.
Fibrinolytic bleeding may frequently be associated with surgical complications following heart surgery (with or without cardiac bypass procedures), and portacaval shunt; hematological disorders such as aplastic anemia; acute and life-threatening abruptio placentae; hepatic cirrhosis; and neoplastic disease such as carcinoma of the prostate, lung, stomach, and cervix.
Urinary fibrinolysis, usually a normal physiological phenomenon, may frequently be associated with life-threatening complications following severe trauma, anoxia, and shock. Symptomatic of such complications is surgical hematuria (following prostatectomy and nephrectomy) or nonsurgical hematuria (accompanying polycystic or neoplastic diseases of the genitourinary system). (See **WARNINGS**.)

CONTRAINDICATIONS

Aminocaproic acid should not be used when there is evidence of an active intravascular clotting process.
When there is uncertainty as to whether the cause of bleeding is primary fibrinolysis or disseminated intravascular coagulation (DIC), this distinction must be made before administering Aminocaproic Acid Injection.
The following tests can be applied to differentiate the two conditions:

- Platelet count is usually decreased in DIC but normal in primary fibrinolysis.
- Protamine paracoagulation test is positive in DIC; a precipitate forms when protamine sulfate is dropped into citrated plasma. The test is negative in the presence of primary fibrinolysis.

• The euglobulin clot lysis test is abnormal in primary fibrinolysis but normal in DIC.

Aminocaproic Acid Injection must not be used in the presence of DIC without concomitant heparin.

WARNINGS

In patients with upper urinary tract bleeding, aminocaproic acid administration has been known to cause intrarenal obstruction in the form of glomerular capillary thrombosis or clots in the renal pelvis and ureters. For this reason, Aminocaproic Acid Injection, USP should not be used in hematuria of upper urinary tract origin, unless the possible benefits outweigh the risk.

Subendocardial hemorrhages have been observed in dogs given intravenous infusions of 0.2 times the maximum human therapeutic dose of aminocaproic acid and in monkeys given 8 times the maximum human therapeutic dose of aminocaproic acid.

Fatty degeneration of the myocardium has been reported in dogs given intravenous doses of aminocaproic acid at 0.8 to 3.3 times the maximum human therapeutic dose and in monkeys given intravenous doses of aminocaproic acid at 6 times the maximum human therapeutic dose.

Rarely, skeletal muscle weakness with necrosis of muscle fibers has been reported following prolonged administration. Clinical presentation may range from mild myalgias with weakness and fatigue to a severe proximal myopathy with rhabdomyolysis, myoglobinuria, and acute renal failure. Muscle enzymes, especially creatine phosphokinase (CPK) are elevated. CPK levels should be monitored in patients on long-term therapy. Aminocaproic Acid Injection administration should be stopped if a rise in CPK is noted. Resolution follows discontinuation of Aminocaproic Acid Injection; however, the syndrome may recur if Aminocaproic Acid Injection is restarted.

The possibility of cardiac muscle damage should also be considered when skeletal myopathy occurs. One case of *cardiac* and *hepatic lesions* observed in man has been reported. The patient received 2 g of aminocaproic acid every 6 hours for a total dose of 26 g. Death was due to continued cerebrovascular hemorrhage. Necrotic changes in the heart and liver were noted at autopsy.

PRECAUTIONS

General

Aminocaproic Acid Injection, inhibits both the action of plasminogen activators and to a lesser degree, plasmin activity.

The drug should NOT be administered without a definite diagnosis and/or laboratory finding indicative of hyperfibrinolysis (hyperplasminemia).*

Rapid intravenous administration of the drug should be avoided since this may induce hypotension, bradycardia, and/or arrhythmia.

Inhibition of fibrinolysis by aminocaproic acid may theoretically result in clotting or thrombosis. However, there is no definite evidence that administration of aminocaproic acid has been responsible for the few reported cases of intravascular clotting which followed this treatment. Rather, it appears that such intravascular clotting was most likely due to the patient's pre-existing clinical condition, e.g., the presence of DIC. It has been postulated that extravascular clots formed *in vivo* may not undergo spontaneous lysis as do normal clots.

Reports have appeared in the literature of an increased incidence of certain neurological deficits such as hydrocephalus, cerebral ischemia, or cerebral vasospasm associated with the use of antifibrinolytic agents in the treatment of subarachnoid hemorrhage (SAH). All of these events have also been described as part of the natural course of SAH, or as a consequence of diagnostic procedures such as angiography. Drug relatedness remains unclear.

Thrombophlebitis, a possibility with all intravenous therapy, should be guarded against by strict attention to the proper insertion of the needle and the fixing of its position.

Epsilon-aminocaproic acid should not be administered with Factor IX Complex concentrates or Anti-Inhibitor Coagulant concentrates, as the risk of thrombosis may be increased.

Laboratory Tests

The use of Aminocaproic Acid Injection, USP should be accompanied by tests designed to determine the amount of fibrinolysis present. There are presently available: (a) general tests such as those for the determination of the lysis of a clot of blood or plasma; and (b) more specific tests for the study of various phases of fibrinolytic mechanisms. These latter tests include both semiquantitative and quantitative techniques for the determination of profibrinolysin, fibrinolysin, and antifibrinolysin.

Drug Laboratory Test Interactions

Prolongation of the template bleeding time has been reported during continuous intravenous infusion of Aminocaproic Acid Injection at dosages exceeding 24 g/day. Platelet function studies in these patients have not demonstrated any significant platelet dysfunction. However, *in vitro* studies have shown that at high concentrations (7.4 mMol/L or 0.97 mg/mL and greater) EACA inhibits ADP and collagen-induced platelet aggregation, the release of ATP and serotonin, and the binding of fibrinogen to the platelets in a concentration-response manner. Following a 10 g bolus of Aminocaproic Acid Injection, transient peak plasma concentrations of 4.6 mMol/L or 0.60 mg/mL have been obtained. The concentration of aminocaproic acid necessary to maintain inhibition of fibrinolysis is 0.99 mMol/L or 0.13 mg/mL. Administration of a 5 g bolus followed by 1 to 1.25 g/hr should achieve and sustain plasma levels of 0.13 mg/mL. Thus, concentrations which have been obtained *in vivo* clinically in patients with normal renal function are considerably lower than the in vitro concentrations found to induce abnormalities in platelet function tests. However, higher plasma concentrations of aminocaproic acid may occur in patients with severe renal failure.

Carcinogenesis, Mutagenesis, Impairment of Fertility
Long-term studies in animals to evaluate the carcinogenic potential of aminocaproic acid and studies to evaluate its mutagenic potential have not been conducted. Dietary administration of an equivalent of the maximum human therapeutic dose of aminocaproic acid to rats of both sexes impaired fertility as evidenced by decreased implantations, litter sizes and number of pups born.

Pregnancy
Pregnancy Category C. Animal reproduction studies have not been conducted with aminocaproic acid. It is also not known whether aminocaproic acid can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Aminocaproic Acid Injection should be given to a pregnant woman only if clearly needed.

Nursing Mothers
It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when aminocaproic acid is administered to a nursing woman.

Pediatric Use
Safety and effectiveness in pediatric patients have not been established.

ADVERSE REACTIONS
Aminocaproic Acid Injection is generally well tolerated. The following adverse experiences have been reported:
General: Edema, headache, malaise.
Hypersensitivity Reactions: Allergic and anaphylactoid reactions, anaphylaxis.
Local Reactions: Injection site reactions, pain and necrosis.
Cardiovascular: Bradycardia, hypotension, peripheral ischemia, thrombosis.
Gastrointestinal: Abdominal pain, diarrhea, nausea, vomiting.
Hematologic: Agranulocytosis, coagulation disorder, leukopenia, thrombocytopenia.
Musculoskeletal: CPK increased, muscle weakness, myalgia, myopathy (see **WARNINGS**), myositis, rhabdomyolysis.
Neurologic: Confusion, convulsions, delirium, dizziness, hallucinations, intracranial hypertension, stroke, syncope.
Respiratory: Dyspnea, nasal congestion, pulmonary embolism.
Skin: Pruritus, rash.
Special Senses: Tinnitus, vision decreased, watery eyes.
Urogenital: BUN increased, renal failure. There have been some reports of dry ejaculation during the period of Aminocaproic Acid Injection treatment. These have been reported to date only in hemophilia patients who received the drug after undergoing dental surgical procedures. However, this symptom resolved in all patients within 24 to 48 hours of completion of therapy.

OVERDOSAGE
A few cases of acute overdosage with Aminocaproic Acid Injection administered intravenously have been reported. The effects have ranged from no reaction to transient hypotension to severe acute renal failure leading to death. One patient with a history of brain tumor and seizures experienced seizures after receiving an 8 gram bolus injection of Aminocaproic Acid Injection. The single dose of Aminocaproic Acid Injection causing symptoms of overdosage or considered to be life-threatening is unknown. Patients have tolerated doses as high as 100 grams while acute renal failure has been reported following a dose of 12 grams.
The intravenous and oral LD_{50} of aminocaproic acid were 3 and 12 g/kg respectively, in the mouse and 3.2 and 16.4 g/kg respectively in the rat. An intravenous infusion dose of 2.3 g/kg was lethal in the dog. On intravenous administration, tonic-clonic convulsions were observed in dogs and mice.
No treatment for overdosage is known, although evidence exists that aminocaproic acid is removed by hemodialysis and may be removed by peritoneal dialysis. Pharmacokinetic studies have shown that total body clearance of aminocaproic acid is markedly decreased in patients with severe renal failure.

DOSAGE AND ADMINISTRATION
Intravenous
Aminocaproic Acid Injection, USP is administered by infusion, utilizing the usual compatible intravenous vehicles (e.g., Sterile Water for Injection, Sodium Chloride for Injection, 5% Dextrose or Ringer's Injection). Although Sterile Water for Injection is compatible for intravenous injection the resultant solution is hypo-osmolar. RAPID INJECTION OF AMINOCAPROIC ACID INJECTION UNDILUTED INTO A VEIN IS NOT RECOMMENDED.
For the treatment of acute bleeding syndromes due to elevated fibrinolytic activity, it is suggested that 16 to 20 mL (4 to 5 g) of aminocaproic acid in 250 mL of diluent be administered by infusion during the first hour of treatment, followed by a continuing infusion at the rate of 4 mL (1 g) per hour in 50 mL of diluent. This method of treatment would ordinarily be continued for about 8 hours or until the bleeding situation has been controlled.
Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Do not administer unless the solution is clear and seal is intact. Discard unused portion.

HOW SUPPLIED

Aminocaproic Acid Injection, USP is supplied in single-dose containers as follows:
5 g/20 mL (250 mg/mL) aminocaproic acid, 20 mL in 30 mL Fliptop Vial (NDC 0409-4346-73, List No. 4346).
Store at 20 to 25°C (68 to 77°F). [See USP Controlled Room Temperature.]

REFERENCES

* Stefanini, M. and Dameshek, W.: The Hemorrhagic Disorder, Ed. 2, New York. Grune and Stratton, pp. 510-514, 1962.

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